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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,488	03/01/2004	Matthew L. Sherman	AM-101314USA	9527

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EXAMINER	
BETTON, TIMOTHY E	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/790,488	SHERMAN ET AL.	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38 and 45-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38 and 45-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant Remarks filed on 28 August 2008 has been acknowledged and duly made of record.

The essence of applicants' arguments are drawn to the alleged improperness directed to the 112, 1st paragraph. Applicants' assert that the Pelosi reference is limited to discussion of a rare tumor type. However, applicants' disclosure is not limited to general types or certainly does not exclude rare types of cancer. Thus, the Pelosi reference is proper. Due to the well-established nature of unpredictability with general cancers alone, the Pelosi reference adequately addresses unpredictability in the art drawn to treating and mitigating cancer.

Further, with regard to applicants' arguments concerning the Dukart et al. reference, the Dukart reference is hereby withdrawn.

Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 1-38 and 45-48 are pending for further prosecution on the merits. Claim 49 is newly added.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim1-38 and 45-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Lane et al.

Lane et al. teach [a] method for the treatment of a disease associated with deregulated angiogenesis in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of **rapamycin** or a derivative thereof, e.g. **CCI779**, ABT578 or a compound of formula I (para. 20).

CCI779 is 42-O-(2-hydroxy) ethyl rapamycin (para. 125).

The term **"aromatase inhibitor"** as used herein relates to a compound which inhibits the estrogen production, i.e. the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, […], and **letrozole**. […] Letrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark FEMARA.TM. or FEMAR.TM. […] A **combination** of the invention comprising a chemotherapeutic agent which is an **aromatase inhibitor** is particularly useful for the treatment of hormone receptor positive tumors, e.g. **breast tumors (para 49)**.

Lane et al teach "lymphatic cancer" [which] are […] tumors of blood and lymphatic system (e.g. Hodgkin's disease, Non-Hodgkin's lymphoma, Burkitt's lymphoma, AIDS-related lymphomas, malignant immunoproliferative diseases, multiple myeloma and **malignant plasma cell neoplasms**, lymphoid leukemia, myeloid leukemia, acute or chronic lymphocytic leukemia, monocytic leukemia, other leukemias of specified cell type, leukemia of unspecified cell type, other and unspecified malignant neoplasms of lymphoid, haematopoletic and related tissues, for example diffuse large cell lymphoma, T-cell lymphoma or cutaneous T-cell lymphoma) [0037].

Further Lane et al teach the administration of a pharmaceutical combination of the invention results not only in a beneficial effect, e.g. a synergistic therapeutic effect, e.g. with regard to slowing down, arresting or reversing the neoplasm formation or a longer duration of tumor response, but also in further surprising beneficial effects, e.g. less side-effects, an improved quality of life or a decreased mortality and morbidity, compared to a monotherapy applying only one of the pharmaceutically active ingredients used in the combination of the invention, in particular in the treatment of a tumor that is refractory to other chemotherapeutics known as anti-cancer agents. In particular, an increased up-take of the co-agent (b) in tumor tissue and tumor cells is observed, when applied in combination with the first agent (a) [0118].

Lane et al. teach By "solid tumors" are meant tumors and/or metastasis (whereever located) other than lymphatic cancer, e.g. brain and other central nervous system tumors (eg. tumors of the meninges, brain, spinal cord, cranial nerves and other parts of central nervous system, e.g. glioblastomas or medulla blastomas); **head and/or neck cancer/breast tumors**; circulatory system tumors (e.g. heart, mediastinum and pleura, and other intrathoracic organs, **vascular tumors and tumor-associated vascular tissue**); excretory system tumors (e.g. kidney, **renal** ,pelvis, ureter, bladder, **other and unspecified urinary organs**); gastrointestinal tract tumors (e.g. **oesophagus**, stomach, small intestine, **colon, colorectal**, rectosigmoid junction, rectum, anus and anal canal), **tumors involving the liver and intrahepatic bile ducts, gall bladder, other and unspecified parts of binary tract, pancreas, other and digestive organs); head and neck; oral cavity (lip, tongue, gum, floor of mouth, palate, and other parts of mouth, parotid gland, and other parts of the salivary glands, tonsil, oropharynx, nasopharynx, pyriform sinus, hypopharynx, and other sites in the lip, oral cavity and**

pharynx); reproductive system tumors (e.g. vulva, vagina, Cervix uteri, Corpus uteri, uterus, ovary, and other sites associated with female genital organs, placenta, penis, prostate testis, and other sites associated with male genital organs); respiratory tract tumors (e.g. nasal cavity and middle ear, accessory sinuses, larynx, trachea, bronchus and **lung**, e.g. **small cell lung cancer or non-small cell lung cancer)**; skeletal system tumors (e.g. bone and articular cartilage of limbs, bone articular cartilage and other sites); skin tumors (e.g. **malignant melanoma of the skin**, non-melanoma skin cancer, basal cell carcinoma of skin, squamous cell carcinoma of skin, mesothelioma, Kaposi's sarcoma); and tumors involving other tissues including peripheral nerves and autonomic nervous system, connective and soft tissue, retroperitoneum and peritoneum, eye and adnexa, thyroid, adrenal gland and other **endocrine glands and related structures, secondary and unspecified malignant neoplasms of lymph nodes, secondary malignant neoplasms of respiratory and digestive systems and secondary malignant neoplasms of other sites** (para. 17).

Lane et al. further teach sub-therapeutic effective amounts of the combination therapy in the treatment of rat pancreatic tumors, i.e., subcutaneous injection of a tumor cell suspension (para. 0088)

Thus, Lane et al. teach each and every limitation of the current invention. Lane et al anticipate the chemotherapeutic combination of CCI-779 and letrozole.

The teachings of Lane et al. further anticipate the variable manifestations and disorders associated with neoplasms and cancer.

Further, with the method of treating a neoplasm with CCI-779 and an aromatase inhibitor, the inherency of therapeutic parameters upon cancerous cells of the mammal body are art-known. Inherently, the combination of two chemotherapeutic agents that are well-known to treat variable forms of cancer individually are anticipated to achieve greater modes of treatment in combination together.

The variable cancerous disease states with similar etiologies are expected to inherently be related by the same general etiologies and that reasonably similar or exact treatments are expected to treat the same.

Claim Rejection- 35 USC §112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 7-38, and 45-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of breast cancer using the claimed combinations, does not reasonably provide enablement for treatment of all neoplasms of any type. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Exparte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988).

The factors to be considered in determining whether undue experimentation is required include:

1) the quantity of experimentation necessary
2) the amount of direction or guidance provided
3) the presence or absence of working examples
4) the nature of the invention
5) the state of the art
6) the relative skill of those in the art
7) the predictability of the art and
8) the breadth of the claims

The Board also stated that the level of skill in the pertinent art is high; the results of experimentation in treating a neoplasm in a mammal in need thereof are unpredictable. While all these factors are considered, a sufficient amount for a prima facie case is discussed below:

The nature of the invention

This invention relates to the treatment of neoplasms.

The amount of direction or guidance provided

The amount of direction or guidance provided is insufficient in regard to a proper explanation as to how treatment directed toward neoplasms of any type. The instant specification discloses general extrapolations of the subject matter of claimed invention. Quantitative direction and/or guidance is lacking in view of the scope and variable susceptibilities of claimed invention.

The quantity of experimentation necessary and state of the art

The quantity of experimentation necessary is high. Further studies, research and development are required due to insufficient evidence in the instant specification to support a proper scope of enablement of current invention. The instant specification discloses no such examples of experimentation. The experimentation yields no quantifiable evidence (comparative data of disclosure of studies on various etiologies of neoplasms or neoplasm types via due experimentation).

The presence or absence of working example

A practicing working example disclosing an embodiment of the central issue of invention directed toward a method of treating any neoplasm type is absent.
One of ordinary skill in the pertinent art would not be readily inclined to reasonably envision the scope of enablement in view of the two examples disclosed within the instant specification.

The predictability in the art

The level of unpredictability is high in the art. The instant specification does not support the due experimentation necessary for the embodiments of claimed invention to be predictable.

For example, the term neoplasm/solid tumor encompasses three distinctly different categories of tumors: (1) sarcomas, those that arise from connective or supporting tissues, such as bone or muscle; (2) carcinomas, those that arise from glandular tissues and epithelial cells;

and (3) lymphomas, those that arise from the lymphoid organs, such as the lymph nodes, spleen or thymus. There are distinct etiologies and pathophysiological differences between these three categories of solid tumor which would not have imbued the skilled artisan with a reasonable expectation of success in treating any one or more of these neoplasm types.

The pertinent art still deems neoplasmic conditions/solid tumors as unpredictable in their clinical behavior (Giuseppe et al., Pulmonary Epithelial-Myoepithelial Tumor of Unproven Malignant Potential: Report of a case and Review of the Literature, Mod Pathol (2001), 14(5): 521-526, printed pages 1-8, especially page 2, immediate paragraph under Full Table).

Further, it is art-known that breast cancer progresses through 4 distinct stages which suggest that treatment modalities may be altered or altogether changed. The specification is absent of any embodiment drawn to the consideration of methodized use in a specific target population with specific individualized parameters. The use as defined in the specification is not commensurate in scope with the scope and content of art-known procedures for treating breast cancer.**THE FOUR STAGES OF BREAST CANCER**

Staging the breast cancer provides some general guidelines to help the doctor decide what type of treatment has the best chance of curing the disease. The National Cancer Institute has developed the following criteria for classifying the extent of breast cancer:

Stage	Extent
I	The tumor is no larger than 2 centimeters (about 1 inch), and the cancer has not spread beyond the breast.
II	The tumor is 2 to 5 centimeters (about 1 to 2 inches), and/or the cancer has spread to the lymph nodes under the arm.
III	The tumor is larger than 5 centimeters (two inches), the cancer involves more of the underarm lymph nodes, and/or the cancer has spread to other tissues near the breast.
IV	The cancer has spread to other organs in the body, most often to the bones, liver, lungs, or brain.

Tripathy, Debu MD Breast Journal. OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF BREAST DISEASE, THE SENOLOGIC INTERNATIONAL SOCIETY, AND

THE INTERNATIONAL SOCIETY OF BREAST PATHOLOGY. 11(1) Supplement: S30-S35, January/February2005 teach [t]argeted therapeutic agents in **breast cancer** are representing a larger proportion of new drugs entering clinical testing. Carcinogenesis is a multistep process characterized by genetic alterations that influence key cellular pathways involved in growth and development. Therefore, there are numerous opportunities for pharmacologic targeting. Hormonal therapy is the prototype of a treatment targeting hormone receptors, and this class of drugs still provides the greatest overall impact on outcome. Even though chemotherapy is considered a cytotoxic and nonspecific therapy, it does modulate many key cellular pathways and therefore shares characteristics of biologic drugs. It is clear that targeted therapies are going to play a greater role in improving survival and quality of life in advanced breast cancer, with trastuzumab (Herceptin) serving as a successful model that is a relatively nontoxic agent associated with survival benefits. **However, several challenges to the successful identification and application of therapeutic targets remain. These include the dissection of complicated and interacting biologic pathways and the limitations of preclinical models that will allow for a better prioritization of which drugs and combinations will succeed best in the clinic. Better methods for selecting ideal candidates for therapy need to be based on known modes of action. Mechanisms of intrinsic and acquired resistance need further exploration in order to refine drug design. Toxicities that might result from modulation of the targeted pathway must be expected and fully characterized. Some biologic strategies may need to be tested in less refractory cases, or even in early stages, even though this may be more costly and could raise safety concerns. Fortunately progress in all of these areas is expected with the availability of new technologies and a growing infrastructure for preclinical and clinical**

testing (abstract only).

Thus, Tripathy D. adequately addresses the concern of *treating neoplasms generally* (applicants' Remarks, page 9, 1st six lines). Further, Tripathy D., discloses challenges which are well-known in the art of chemotherapeutic treatment. The scope of enablement in this current invention depends on a reasonable use of these compounds as disclosed. Unpredictability remains high in view of the claimed invention based on the disclosure of Examples 1 and 2 which are deficient in explaining and elucidating the scope of the invention. The Examples disclose no cumulative results or correlative data further suggesting that the claims of the current invention were achieved.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner signing this action, James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624
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